

THE GRADUATE COLLEGE OF THE  
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

**MAGGIE LEONA YODER**

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE  
GRADUATE COLLEGE  
DEPARTMENT OF CELL BIOLOGY

Monday, December 12, 2016, 2:00 p.m.  
Room 109, Biomedical Research Center, OUHSC

**Multisystem Effects of Usher Syndrome Type 2A**



COMMITTEE IN CHARGE: *Muna Naash, Ph.D., Chair, Lawrence Rothblum, Ph.D., Co-Chair, Ralf Janknecht, Ph.D., David Sherry, Ph.D., H. Anne Pereira, Ph.D., Gary Gorbsky, Ph.D., and Guangpu Li, Ph.D.*

**ABSTRACT:** Usher syndrome (USH) is a disease that leads to combined deafness/blindness via an unknown mechanism. To understand the underlying mechanism, we developed an USH2A knockin (KI) mouse expressing an usherin human disease mutation, c.2299delG. My work focuses on the audiovisual characterization of this model and extends the current knowledge of expression of *Ush2a* in organs outside the retina and cochlea.

In the audiovisual systems, I determined that the *Ush2a* mutation generates a stable truncated transcript and protein, which is expressed in photoreceptors and hair cells. Expression of the truncated protein in the retina leads to age-dependent degenerative changes evident by loss of visual function, delayed light-dependent transducin/arrestin translocation, early onset-delay in rod recovery after photobleach, and increased rod sensitivity. Co-immunoprecipitation confirmed that the increased rod sensitivity is due to delay in  $\alpha$ -transducin translocation upon light exposure; in turn increasing its availability to re-associate with  $\beta$ -transducin and initiate signal transduction. Interestingly, KI mice reared under a higher intensity cyclic light (HL) rescued the delay in scotopic recovery and arrestin translocation. This rescue was only possible when mice were reared under HL from birth, implicating a developmental effect. In the cochlea, this usherin mutation led to abnormal stereocilia organization.

I have used GFP to assess tissue specific *Ush2a* promoter activity and revealed its presence in multiple tissues outside the audiovisual systems including lung, ovary and brain. Analysis of reproduction showed reduced numbers of pups born per KI litter, and further investigation revealed increased autofluorescent deposits in the ovary. Most interestingly, usherin expression was found in brain ependymal cells accompanied by behavioral abnormalities consistent with schizophrenia, which has been implicated in some USH patients.

Taken together my work has expanded the field of USH by characterizing the first mouse model with late onset retinal degeneration and finding that usherin is critical in maintaining and/or regulating phototransduction. Additionally, my work shows a potential genetic link between USH and schizophrenia that has previously been attributed to loss of visual and auditory capabilities. Further characterization of this model is necessary to better understand the human disease and to develop therapies for treatment.